Author’s response to reviews

Title: Quality of survival among symptomatic compared to PSA-detected prostate cancer survivors - Results from a UK wide patient-reported outcomes study

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Version: 1 Date: 08 Jul 2019

Author’s response to reviews:
Thank you to both reviewers for taking the time to review the article and provide useful feedback. We have addressed each comment below. Modifications to the manuscript based upon reviewer comments have been added using tracked changes. In the event that reviewer queries are already answered in the manuscript, we have highlighted those points in yellow.

Reviewer 1

The authors are to be commended for completing this huge population-based study. The paper is generally well written and addresses an important subject.

Thank you for the positive comments and the feedback provided.

I have one main concern and few minor points (all listed below)

1.1 My main concern is the study's conclusion which does not seem to be supported by the study findings and its limitations (many of them, but not all, are acknowledged by the authors in their discussion). The conclusion needs to be amended to reflect the evidence.

Response: Other than highlighting the quality of life differences between symptomatic and PSA-tested prostate cancer survivors, the two main conclusions refer to the possible need for additional aftercare and inclusion of method of presentation in prostate cancer outcome studies. We have attempted to reword the conclusion section in the abstract and discussion to more clearly show the connection between the results and these recommendations. See also the response to reviewer comment 2.18. [Abstract Page 2 Line 59; Conclusions Page 16 Line 15]

1.2 Gleason score needs to be explained/ introduced to justify score categories used and to help readers with no subject-specific expertise.

Response: A description of the Gleason score categories has been added to the methods section. [Methods Page 7 Line 59]

1.3 Since the study included survivors 18-42 months post-diagnosis and considering that functional outcomes could change over-time, was time since diagnosis included as a covariate?

Response: Time since diagnosis wasn’t used as an independent predictor in the model, thus the comment raised by the reviewer is a valid concern addressing a complex issue. The time frame of 18-42 months was initially chosen because it represents the period when initial treatment is complete and side-effects and quality of life have begun to stabilise(a). We have added this reason for why 18-42 months was chosen to the methods. [Methods Page 6 Line 27]
Despite this we attempted to acquire information on time since diagnosis from the cancer registries in each country, but were unable to do so in England. Fortunately, after looking at the outcomes by time since diagnosis in Northern Ireland we were able to confirm that outcomes were reasonably stable within the 18-42 month period, meaning that time since diagnosis is unlikely to influence the results.

Functional outcome scores by time since diagnosis (Northern Ireland only)

<table>
<thead>
<tr>
<th>Time since diagnosis</th>
<th>Self-assessed health</th>
<th>Urinary incontinence</th>
<th>Urinary irritation</th>
<th>Bowel function</th>
<th>Sexual function</th>
<th>Hormonal function</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-23 months</td>
<td>76.7</td>
<td>83.8</td>
<td>84.8</td>
<td>84.5</td>
<td>22.1</td>
<td>74.1</td>
</tr>
<tr>
<td>24-29 months</td>
<td>75.9</td>
<td>84.7</td>
<td>83.7</td>
<td>87.0</td>
<td>25.2*</td>
<td>78.8*</td>
</tr>
<tr>
<td>30-35 months</td>
<td>74.2</td>
<td>81.4</td>
<td>81.5*</td>
<td>84.7</td>
<td>21.5</td>
<td>72.1</td>
</tr>
<tr>
<td>36-42 months</td>
<td>74.5</td>
<td>83.9</td>
<td>84.3</td>
<td>83.6</td>
<td>22.5</td>
<td>76.7</td>
</tr>
</tbody>
</table>

Adjusted for age, deprivation, number of comorbidities and treatment type

*p<0.05, **p<0.001 – compared to baseline (18-23 months).


1.4 Introduction page 5 line 1-3 need clarification especially of what "this analysis" refers to.

Response: We have reworded this sentence for clarity. [Introduction Page 5 Line 19]
1.5 In the results section: clarify how the 9% with alternative or unknown presentation were treated in the analysis. It seems that they were excluded, however, this needs to be clarified.

Response: The men who presented with an alternative/unknown method of presentation were excluded from the analysis. We have added this point to the results section. [Results Page 10 Line 20]

1.6 Based on the above point, you want to amend the final number reported in the first paragraph of the discussion to reflect number of patients used in the analysis.

Response: We have added this value to the first paragraph of the results section. [Results Page 10 Line 25]

1.7 A reference to the original aims of the study and its main findings published very recently would help put the present article and its results in context.

Response: The final paragraph of the introduction has been expanded to reflect this and include references to the original study. [Introduction Page 5 Line 27]

Reviewer 2

Thank you for inviting me to review the manuscript which investigates quality of survival among symptomatic compared to PSA-detected prostate cancer survivors.

Thank you for your comments on the manuscript. The changes made as a result of your feedback improve the clarity and readability of the article.

Background

2.1 It would be helpful for understanding the problematic of the topic to see the numbers about how many men are presented either symptomatically or by a PSA test in UK and Europe/worldwide.

Response: We agree that this would be helpful information. However, this exact information is not available in the UK. Even the recent National Prostate Cancer Audit only included PSA information on prostate cancer patients post diagnosis. However, we have added some information on PSA testing rates, referral rates, and the proportion of these who are diagnosed with prostate cancer in England. [Introduction Page 4 Line 22]
2.2 Please add statistics about how many men are requesting a PSA-test in UK, to emphasize the relevance of the research question.

Response: See response to comment 2.1.

2.3 Please state the rational for using the term «quality of survival» instead of «quality of life».

Response: We have replaced the term “quality of survival” with “quality of life” throughout the manuscript. [Throughout manuscript]

2.4 The term «survival prospects» is very vague. Do you mean overall 5/10 year-survival, cancer-free survival…?

Response: The term “survival prospects” has been replaced with the terms used in the original references. [Introduction Page 5 Line 7]

2.5 The rationale behind the research question should be more emphasized.

Response: The final paragraph of the introduction has been expanded to reflect this. [Introduction Page 5 Line 27]

Methods/Results

2.6 The authors describe that questions were divided into the corresponding domains, answers linearly transformed, and summary scores calculated. Please add here the corresponding guidelines.

Response: A reference to scoring instructions has been added. [Methods Page 7 Line 36]

2.7 Moreover, the authors described that reported prevalence of experiencing specific problems was based upon the proportion of men reporting moderate/big problems (…). Please add the guidelines/methodological standards based on which the authors performed this dichotomization, because dichotomization of scores can lead to loss of information. Additionally, please indicate whether the EPIC-26 can be used for comparisons based on items scores.

Response: The EPIC-26 summary scores themselves were not dichotomised in this study. The proportion of men reporting moderate/big problems comes from recoding the original five responses to the questions into two categories (moderate/big, none/small/very small). This approach has been used previously. We have highlighted this in the methods section with reference to the use of this approach in the past. The EPIC-26 scores have been widely used for comparative purposes in prostate cancer outcome studies. [Methods Page 7 Line 29]
2.8 Where the results adjusted for multiple testing? (Pe et al., Lancet Oncol 2018) This issue is especially relevant for the item-based comparisons.

Response: Thank you for highlighting this issue. We have applied this correction to the results and included reference to it in the methods. Given the statistical power of the study this has resulted in minor modifications and did not change the conclusions. [Methods Page 9 Line 19, Table 3, Supplementary table 5]

2.9 For clinicians and patients it is very important to understand whether differences in Epic-26 scores between groups are clinically relevant. That's why the authors should define in the methods the definition they used to assess clinically relevance and state whether your found differences were clinically relevant or not.

Response: We agree that the issue of clinical relevance is very important, but would be of the opinion that it relates more to how the results are interpreted and thus belongs in the discussion section. We have added an additional paragraph to the discussion on this issue, with reference to how we have determined clinical relevance. [Discussion Page 15 Line 36]

2.10 Table 1/ Sup Table 2: Please add results of significance tests comparing all groups and make a statement, if and how PC survivors differ by method or presentation.

Response: The distribution of all socio-demographic and clinical characteristics included in these tables varies significantly (p<0.001) by method of presentation. We have added this to the text rather than repeat the same information in the tables. [Results Page 10 Line 15]

2.11 Table Sup 4: On which sig. tests are the p-values based? Would it not be interesting to understand whether for example urinary continence differs by method of presentation for each stratum?

Response: The p-value is based upon ANOVA – A footnote for this is included with the table and is mentioned in the methods. The results are also presented in this table for each clinical subgroup (age, stage, Gleason score, and treatment). [Methods Page 8 Line 48]

2.12 What is the average time since diagnosis of this cohort? That needs to be shown in the results. And why was time since diagnosis not considered as a confounding variable?

Response: We refer to the response to comment 1.3.
2.13 Why were employment status, ethnicity, marital status and number of comorbidities not displayed on tables 1, 2/3 and presented in the results? Why were these factors not considered as potential confounding variables? Several studies showed in the past the importance of these variables in explaining differences in patient reported outcomes, especially functional outcomes.

Response: These variables were included in the multivariable analysis. They are listed in the methods section and in the footnotes of table 1. They are not displayed in table 1 for space reasons, but are included in supplementary table 2 (with a reference to them in the text – We have also added a footnote to table 1 to highlight the existence of this data). The additional variables are not relevant to tables 2 and 3 as these variables are used for adjustment purposes only and do not form part of the objectives of the analysis. [Methods Page 9 Line 1]

2.14 Why is the item "problems with bloody stools" the only one, which does not significantly differ by method or representation?

Response: This is likely a result of the low reported frequency of this problem. We have added this to the text which reports this result. [Results Page 11 Line 9]

Discussion

2.15 Is the proportion of involved PC survivors presenting via a PSA test common in UK and globally?

Response: Unfortunately we are unable to evaluate this due to the unavailability of this information in the UK.

2.16 It remains unclear whether the found results are similar or not to the results of the previous performed study of Drummond et al.

Response: The Drummond et al study did not include adjustments for treatment and socio-demographic factors. However, the univariate results in their study also showed functional differences by method of presentation similar to ours. We have clarified that in the text. [Discussion Page 13 Line 46]
2.17 The paragraph (page 12) about clinical differences between PC survivors presented by a PSA test or clinically is very speculative. Therefore, it is needed to compare the results of this study with the results of previous studies assessing health behaviour patterns or predictors of attendance patterns related to PC screening.

Response: See response to comment 2.9 for the issue of clinical relevance. With regards the second part, this is an interesting idea, but seems to relate more to the issue of whether or not men are PSA-detected or symptomatic rather than their quality of life, which is the aim of this study. It may thus be outside the scope of this paper, with insufficient space allowed for a thorough discussion of these issues. However, thank you for this suggestion.

2.18 The authors need to be more precise in the explanation about why they believe that method of presentation is a key factor in outcomes studies - based on the argumentation on page 12 the rationale behind this strong conclusion remains unclear.

Response: We have expanded the conclusion in the discussion to include the justification for this recommendation. However, we have also changed the wording of the recommendation to suggest that method of presentation should be considered, rather than required, in future studies. [Discussion Page 16 Line 22]

2.19 What is the clinical implication of that study on whether men should do the PSA test or not?

Response: The issue of whether or not men should have a PSA test is complex and involves many different factors. While we believe the information in this article is useful and may provide some further evidence in the debate about PSA testing, we do not feel that the study on its own provides sufficient evidence to make a recommendation for or against men having a PSA test.

2.20 Figure 1: The EPIC-26 questionnaire is not an instrument to assess depression. Please correct that mistake.

Response: While the reviewer is correct in that the EPIC-26 questionnaire is not specifically designed to assess depression, it is a validated survey instrument which does include a single question on this issue that specifically uses the term “feeling depressed”. We have included it in figure 1 in the context of a single item response to the EPIC-26 question set. The title to figure 1 has been modified to reflect this. (Figure 1, Page 24).
2.21 Why does figure 1 show the prevalence of "feeling depressed" and lack of energy, when these issues were not discussed in the paper?

Response: The responses to all 26 questions from the EPIC-26 questionnaire are included in supplementary table S3, with the five specific questions in figure 1 highlighted as they are the questions that give an overall summary of the urinary, bowel, sexual and hormonal domains, with depression and lack of energy part of the hormonal domain. It would be impractical and redundant to describe every difference in the text. However, a general statement “The proportion of PSA-detected men reporting moderate/big problems for each EPIC-26 question was significantly lower than for symptomatic men (p<0.001), with the exception of problems with bloody stools” which refers to these results is included in the text. [Results Page 11 Line 4]

Minor:

2.22 The authors describe that the study of Drummond et al was performed "recent". However, the corresponding paper was published in 2016 and the study was performed in 2011.

Response: The term “A recent study” has been replaced with “Drummond et al”. [Discussion Page 13, Line 47]

2.23 Figure 1: Please indicate whether differences are significantly different also in the figure.

Response: 95% confidence intervals for each proportion are included in the figure. Due to the large size of the study the error bars are small, thus we have added a footnote to highlight their presence and explain what they are. [Figure 1]